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L9: Entry 8 of 49 File: PGPB Nov 7, 2002

DOCUMENT-IDENTIFIER: US 20020164648 A1
TITLE: Methods and compositions for delivery and retention of active agents to lymph nodes

Abstract Paragraph:
The present invention is directed to delivery and retention of active agents to targeted lymph nodes in a mammal using a ligand/anti-ligand pair. More particularly, the invention involves methods, compositions, and kits for delivery and retention of active agents to targeted lymph nodes using compositions comprising a ligand-colloid moiety and compositions comprising an anti-ligand. Active agents may be associated with one or more of the colloid, ligand, or anti-ligand. Conjugation of the ligand and anti-ligand after administration permits retention of aggregated colloid complex in targeted lymph nodes.

Summary of Invention Paragraph:
[0003] The present invention relates generally to delivery and retention of active agents at a targeted site using compositions comprising ligand and anti-ligand conjugates. More particularly, certain embodiments concern methods, compounds, compositions and kits useful for targeted delivery and retention of agents at specific lymph nodes by administration of a composition comprising a ligand-colloid moiety and a composition comprising an anti-ligand. In certain embodiments the ligand is one member of the biotin/avidin pair and the anti-ligand is the other member of the biotin/avidin pair.

Summary of Invention Paragraph:
[0013] Liposomes have been described as potential agents for targeted delivery of diagnostic or therapeutic agents to a wide range of organ systems and diseases. Such targeting is due primarily to a physical feature of the liposome, such as size, charge, and lipid compound, and is not due to specific site-directed targeting. Phillips et al., Handbook of Targeted Delivery of Imaging Agents, CRC Press, 149-173, 1995, incorporated herein in its entirety by reference. Coupling macrophage-specific ligands to the surface of liposomes increases liposome drainage from an interstitial injection site and enhances their localization in regional lymph nodes. Moghimi et al., Prog Biophys Molec Biol 65:221-249, 1996, incorporated herein in its entirety by reference.

Summary of Invention Paragraph:
[0026] In one embodiment, the present invention features a ligand/anti-ligand system and colloids that are captured by draining lymph nodes when administered to a subject in vivo. Ligand or anti-ligand may be conjugated to the colloid. The ligand may be, for example, biotin The anti-ligand may be, for example, avidin.

Summary of Invention Paragraph:
[0027] In another embodiment, the invention features methods of delivering and retaining an active agent at targeted lymph nodes in a mammal. The methods comprise the steps of (a) administering to a mammal a first composition comprising ligand conjugated to a colloid, and (b) administering to a mammal a second composition comprising anti-ligand in which the anti-ligand binds to the ligand. The anti-ligand may be administered proximal to the site of the colloid-ligand conjugate administration. After the anti-ligand binds the ligand of the colloid-ligand

conjugate, the aggregated colloid complex may be retained at the lymph node(s) draining the areas of interest.

Summary of Invention Paragraph:
[0030] In yet another embodiment the invention provides a method and composition for delivering and retaining an active agent at the sentinel lymph node(s) comprising the steps of (a) administering to a mammal a first composition comprising ligand conjugated to a colloid, and (b) administering to a mammal a second composition comprising anti-ligand in which the anti-ligand binds to the ligand. The colloid may comprise an active agent, in particular, a blue dye as a detection means. Anti-ligand, with or without an active agent, that binds to the ligand of the ligand-colloid-blue dye composition, may be administered simultaneously or shortly after the ligand-colloid-blue dye composition is administered to a mammal. The preferred administration method is by subcutaneous injection.

Summary of Invention Paragraph:
[0031] In an embodiment of the detection or therapeutic method of the present invention, the ligand-colloid-active agent can be injected subcutaneously or intracavitary. The preferred dose depends on the species and whether a therapeutic or diagnostic agent is administered. This can be administered as a single injection or in divided doses. Simultaneous with the ligand-colloid composition or after 30 minutes, more preferably at less than 15 minutes and even at less than 10 minutes, a dose of anti-ligand, with or without an active agent, may be administered subcutaneously or intracavitary. The anti-ligand can be given as a single injection or in divided doses, administering the anti-ligand in two doses is preferred in certain circumstances. Within one hour of the last injection, detection of lymph nodes containing the aggregated colloid complex is accomplished using, for example, planar and single-photon emission computed tomography scans made with a gamma camera equipped with the appropriate collimator and selecting the appropriate energy windows for the detection isotope being used, such as 140 keV for Technetium-99m. An important point is that the ligand-colloid continues to accumulate in the lymph node and the colloid is retained in the node for a prolonged time (>20 hours).

Summary of Invention Paragraph:
[0062] The methods, compounds, compositions, and kits of the present invention are advantageous for selective detection and therapy of lymph nodes because of the significant increase in the amount of the detection and/or therapeutic agent which is available at the targeted lymph node due to the increase in retention of the detection and/or therapeutic agent at the targeted lymph node. These methods, compounds, compositions, and kits are an improvement, in terms of absolute amount of detection and/or therapeutic agent retained at the lymph node, as compared to the prior art procedures which do not contemplate the use of ligand/anti-ligand systems to retain colloids in lymph nodes, thereby amplifying the amount of detection and/or therapeutic agents available at the targeted lymph node. The methods of the present invention can be used to detect (either by internal procedures or by external imaging) and/or treat lymph nodes which drain specific body sites. The delivery and retention of therapeutic and/or detection agents at lymph nodes using colloids such as microspheres, microcapsules, emulsions, and liposomes is contemplated.

Summary of Invention Paragraph:
[0063] The present invention greatly increases the uptake and retention of colloids in regional lymph nodes by use of a ligand/anti-ligand system, for example, the biotin/avidin system, to form complexes which are directed to and retained in the lymphatic system. Methods for coupling ligands to colloids, such as liposomes, are known to those of skill in the art. See, for example, Schuber, in Liposomes as Tools in Basic Research and Industry, Philippot and Schuber (eds), CRC Press, Boca Raton, 21-39, 1995, incorporated herein in its entirety by reference. Initial

injection of colloid-ligand followed by subsequent injection of anti-ligand causes binding of ligand and anti-ligand, with cross-linking and consequent aggregation of colloid-ligand that is in the process of migrating through lymphatic vessels. The complex of colloid-ligand-anti-ligand-active agent(s) moves from the site of binding of the ligand and anti-ligand to the lymph and onward to the primary lymph node.

Summary of Invention Paragraph:
[0065] The colloidal particles of the present invention are preferably in the size range 1 to 5,000 nm, more preferably 5-500 nm, and most preferably 50 to 300 nm. Such systems are well transported from the site of injection and are well retained in the lymph nodes (primary and secondary). If the colloid-ligand composition is too large, it is retained at the site of injection. If the colloid-ligand composition is too small, it is transported from the site of injection into the circulation and is not retained in the lymph node(s).

Summary of Invention Paragraph:
[0066] In an embodiment of the method of the present invention, the ligand-colloid-active agent can be administered as a single injection or in divided doses. For example, simultaneous with the ligand-colloid composition or after 2 hours, more preferably at less than 30 minutes and even at less than 10 minutes, a dose of anti-ligand, with or without an active agent, is administered. The anti-ligand composition can be given as a single injection or in divided doses; administering the anti-ligand in two doses is preferred in certain circumstances. The ligand-colloid and anti-ligand compositions are administered by subcutaneous, subdermal, submucosal, intraperitoneal, or intrapleural injection. Within one hour of the last injection, detection of lymph nodes containing the aggregated colloid complex is accomplished. If a radiolabeled detection agent is encapsulated in or attached to the colloid or attached to anti-ligand, detection of the lymph nodes is accomplished using for example, planar and single-photon emission computed tomography scans made with a gamma camera equipped with the appropriate collimator and selecting the appropriate energy windows for the detection isotope being used, such as 140 keV for Technetium-99m. If blue dye is encapsulated in the colloid, the lymph nodes can be visually detected.

Summary of Invention Paragraph:
[0070] The time required for initial localization of the colloid-ligand-anti-ligand composition in the lymph node is generally under 1 hour; however, the colloid-ligand-anti-ligand composition continues to accumulate in lymph node for 24 hours or more. Therefore, therapy or imaging can be accomplished in one short procedure. In addition, localization and retention of the colloid-ligand-anti-ligand composition at specific lymph nodes limits the distribution of the colloid-ligand-anti-ligand composition in the circulation, thus the active agents of the colloid-ligand-anti-ligand composition are unlikely to produce toxic side effects at the levels required for therapy or imaging.

Summary of Invention Paragraph:
[0071] An advantage of the present invention is the flexibility of the system. For example, when a biotin-liposome-avidin complex is utilized, the complex is strongly retained in the targeted lymph node for a prolonged period, at least several days, until it is metabolized. If Technetium-99m, whose half-life is 6 hours, is employed as an active agent, it can still be imaged at least 20 hours after administration. If blue dye is employed as an active agent, lymph nodes may be visually detected at least two weeks after administration. X-ray and computerized axial tomography contrast agents may be detected for a prolonged time period, similar to that for detection of blue dye.

Summary of Invention Paragraph:
[0075] The colloid may be associated with an active agent, such as a detection or therapeutic agent. The ligand may be, for example, biotin. The anti-ligand, which

may or may not be associated with an active agent, may be, for example, avidin. The anti-ligand may be administered simultaneously or immediately after administration of the colloid-ligand composition. The anti-ligand may be administered in the same location as the colloid-ligand or it may be administered at another site so that it encounters the colloid-ligand at, or just prior to reaching, the targeted lymph node.

Summary of Invention Paragraph:
[0081] The active agent may be associated with the colloid or anti-ligand by any well known technique, but should be in such a way that the active agent remains associated with the colloid or anti-ligand until the point of uptake of the colloid-ligand-anti-ligand complex by the lymph nodes. The association of the active agent with the colloid includes any method of incorporating the active agent into or grafting the active agent onto the colloid.

Detail Description Paragraph:
[0144] Incorporation of blue dye with the colloid of the aggregated colloid complex of the present invention provides for retention of the blue dye at the first lymph node encountered, or in the chain of draining lymph nodes, depending upon the timing of administration of the anti-ligand-active agent.

Detail Description Paragraph:
[0172] Vaccine adjuvants are agents when given in combination with an antigen, greatly increase the immune response to the antigen. Vaccine adjuvants are essentially antigen delivery systems, however, the mechanisms and locations involved in the delivery of the antigen are poorly understood. Most common adjuvants are colloids. Typical colloids used are aluminum hydroxide colloids and liposome colloids. (See Theory and Practical Application of Adjuvants. Stewart-Tull (ed), John Wiley & Sons Ltd., Chichester, England, 1995, incorporated herein by reference.) The most recent information indicates that antigen delivery to the lymph node and induction of lymph node hypercellularity are important aspects of adjuvant function. Lindblad, in Theory and Practical Application of Adjuvants, Stewart-Tull (ed), John Wiley & Sons Ltd., Chichester, England, pg. 21-35, 1995 and Gregoriadis, in Theory and Practical Application of Adjuvants, Stewart-Tull (ed), John Wiley & Sons Ltd., Chichester, England, pg. 145-169, 1995, incorporated herein in their entirety by reference. Since the essential nature of how vaccine adjuvants work is poorly understood, most vaccine development is conducted by trial and error. These trial and error techniques are inefficient and costly. Much effort is currently being focused on understanding how vaccines work. This work has been spurred by the effort to develop an effective vaccine for treatment and prevention of HIV infection and as an immune stimulant for cancer therapy. Even though vaccine adjuvants are clearly antigen delivery vehicles, virtually no studies have used isotopes or imaging or other detection agents such as dyes to study their biodistribution in the body after administration. If lymph node delivery is important, it will be obvious that the colloid-ligand-anti-ligand system described herein will be very useful for enhancing immune response to an antigen which is delivered to the lymph nodes by this system.

Detail Description Paragraph:
[0175] To demonstrate the use of biotin-colloid/avidin technology to increase the retention of the liposomes in lymph nodes, biotin-liposomes encapsulating only glutathione and labeled using the .sup.99mTc-HMPAO technique were studied. Four rabbits were subcutaneously injected in the foot pads of both feet with .sup.99mTc-biotin-liposomes in 0.3 ml volume. This is an asymmetric study, since only one foot was then subcutaneously injected with 5 mg of avidin in 0.3 ml of saline 5 min after injection of the 99m Tc-biotin-liposomes. The avidin was subcutaneously injected on the right rabbit foot 2 cm proximal from the liposome injection. Scintigraphic imaging with a gamma camera was performed of the rabbits for the first hour after liposome injection and then at 20 hours to follow the movement of the .sup.99mTc-biotin-liposomes in relationship to the avidin. These images are

analyzed by drawing a region of interest around the site of the liposome injection and around the popliteal lymph nodes.

Detail Description Paragraph:
[0178] From the biodistribution studies, it can be seen that the .sup.99mTc-biotin-liposomes are retained in high percentages in the popliteal lymph node on the side in which the avidin was injected. This demonstrates that the use of .sup.99mTc-biotin-liposomes with avidin results in a significantly increased retention of liposomes to the lymph nodes. These results suggest that this method could be used to increase the delivery of liposome encapsulated agents to the lymph nodes.

Detail Description Paragraph:
[0182] Biotin-liposomes labeled with .sup.99mTc can encapsulate blue dye for visually marking the first lymph node encountered. The blue dye can also be considered as an example of drug delivery to a lymph node. Other drugs such as anticancer agents, antiviral agents, vaccines, photodynamic dyes, antibiotics, and therapeutic radionuclides, could also be delivered instead of blue dye.

Detail Description Paragraph:
[0186] To assess the effect of repeat injections on the avidin-induced retention of biotin-liposomes in the popliteal lymph nodes, a study was performed with .sup.99mTc-biotin-liposomes encapsulating blue dye. These studies were asymmetric and performed in the same manner as Example 13 studies, except that the same group of rabbits (n=4) received repeat injections at baseline, 2 wk and 4 wk. Liposomes were injected into the dorsum of both feet with avidin injected 2 cm proximal on the right foot only. Imaging was performed for the first hour and at 20 hr after liposome injection. Biodistribution was performed by scintigraphic imaging alone since tissue sampling was not possible until the end of the third study in each rabbit.

Detail Description Paragraph:
[0190] Results are shown in Table 5. The blue .sup.99mTc-biotin-liposomes passed through the popliteal lymph node with retention equal to control studies, but accumulated in the iliac lymph nodes with significantly greater retention than normal. Iliac lymph nodes had greater liposome accumulation than the popliteal lymph node (3.9 versus 1.45 p=0.003). Images demonstrated the increased accumulation in the iliac lymph node compared to the popliteal lymph node

Detail Description Paragraph:
[0192] To determine if liposomes injected into the peritoneum, followed 30 min later by avidin injected into the peritoneum, would target the lymph nodes that receive lymph that drains from the peritoneum, 2 ml of .sup.99mTc-biotin-liposomes encapsulating blue dye were injected into the peritoneum of experimental (n=4) and control rats (n--4). Thirty minutes after liposome injection, 5 mg of avidin in 1 ml of saline was injected into the peritoneum of the experimental group, while the controls received no avidin.

Detail Description Paragraph:
[0195] A study was performed to determine if .sup.99mTc-blue-biotin liposomes injected into the submucosal tissue of the colon would have increased targeting to the lymph nodes that drain the colon and followed by an avidin injection into submucosal tissue of the colon adjacent to the liposome injection.

Detail Description Paragraph:
[0199] Most carcinomas including colon cancer metastasize first to abdominal lymph nodes. This experiment demonstrates that the lymph nodes draining a region of the colon can be targeted using identification of the cancer with colonoscopic visualization and subsequent injection of the submucosa near the cancer with .sup.99mTc-blue-biotin liposomes and avidin. This could greatly increase the delivery of therapeutic agents such as drugs and therapeutic radionuclides to the

lymph nodes that drain the region of the colon carcinoma.

Detail Description Table CWU:
7TABLE 7 Accumulation of .sup.99mTc-Blue-Biotin Liposomes in Lymph Nodes Draining Colon After Colonoscopic Guided Injection of .sup.99mTc-Blue-Biotin Liposomes into Colonic Submucosa (n = 1) (n = 1) Experimental (+ Avidin) Control (- Avidin) % localized % localized Initial Injection Site 23.45 25.69 Hepatic Node 4.41 0.58 Iliac Node 1.22 not visualized

CLAIMS:

1. A method for delivery and retention of an active agent in one or more targeted lymph nodes, comprising: a) injecting into a mammal a first composition comprising ligand conjugated to a colloid; and a) injecting into said mammal a second composition comprising anti-ligand, wherein said anti-ligand binds to said ligand.

15. A method for detecting one or more sentinel lymph nodes comprising: a) injecting in the vicinity of a tumor in a mammal a first composition comprising ligand conjugated to a colloid; and b) injecting into said mammal a second composition comprising anti-ligand, wherein said anti-ligand binds to said ligand.

20. A kit for delivering and retaining an active agent in one or more lymph nodes, comprising: a) a first composition comprising ligand conjugated to a colloid; and b) a second composition comprising anti-ligand.

L9: Entry 16 of 49 File: USPT Feb 18, 2003

DOCUMENT-IDENTIFIER: US 6521211 B1
TITLE: Methods of imaging and treatment with targeted compositions

Detailed Description Text (127):
Examples of monoclonal antibodies which may be employed as targeting ligands in the present compositions include CALAM 27, which is formed by immunizing BALB/c mice with whole human squamous cell carcinoma of the tongue and forming hybridomas by crossing extracted spleen cells with those of an NS1 syngeneic myeloma cell line. Gioanni, J. et al., Cancer Research, Vol. 47, pp. 4417-4424 (1987). CALAM 27 is directed to surface epitopes of both normal and malignant epithelial cells. Normal lymph nodes generally do not contain cells expressing these epitopes. See Cancer Research, Vol. 47, pp. 4417-4424 (1987). Accordingly, lipid and/or vesicle compositions comprising this antibody can be used to target metastases in the lymph nodes. The monoclonal antibody 3C2 may be employed as a targeting ligand for targeting malignant epithelial cells of serious ovarian carcinoma and endometrioid carcinoma. Another exemplary targeting ligand is Mab 4C7 (see Cancer Research, Vol. 45,2358-2362, 1985), which may be used to target mucinous carcinoma, endometriod carcinoma and mesonephroid carcinoma. For targeting squamous cell carcinoma in head and neck cancer, Mab E48 (Biological Abstract, Vol. 099 Issue. 066 Ref. 082748) may be used as a targeting ligand. For targeting malignant melanoma, the monoclonal antibody 225.28s (Pathol. Biol., Vol. 38 (8), pp. 866-869, 1990) may be employed.

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L19: Entry 10 of 10 File: DWPI Jan 21, 1999

DERWENT-ACC-NO: 1999-120520
DERWENT-WEEK: 199924

TITLE: In vivo transfection of tissue with retinoblastoma gene - formulated with spermine cholesterol carbamate as cationic amphiphile to facilitate transport, used for gene therapy of cancers and tumours

Basic Abstract Text (1):
Transfection of tissues in vivo comprises administering to the patient's vascular or lymphatic systems, or tissue fluid, a composition (A) comprises: (i) DNA encoding retinoblastoma protein (Rb), and (ii) spermine cholesterol carbamate (SSC) as cationic amphiphile, so that (A) contacts the target tissue.

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L24: Entry 31 of 113 File: PGPB Dec 26, 2002

DOCUMENT-IDENTIFIER: US 20020197210 A1
TITLE: Stabilized therapeutic and imaging agents

Detail Description Paragraph:
[0080] In a preferred embodiment, the targeting entity is attached to the stabilizing entity. In one embodiment, the attachment is by covalent means. In another embodiment, the attachment is by non-covalent means. For example, antibody targeting entities may be attached by a biotin-avidin biotinylated antibody sandwich, to allow a variety of commercially available biotinylated antibodies to be used on the coated polymerized liposome. Specific vasculature targeting agents of use in the invention include (but are not limited to) anti-VCAM-1 antibodies (VCAM=vascular cell adhesion molecule); anti-ICAM-1 antibodies (ICAM=intercellular adhesion molecule); anti-integrin antibodies (e.g., antibodies directed against .alpha..sub.v.beta..sub.3 integrins such as LM609, described in International Patent Application WO 89/05155 and Cheresh et al. J. Biol. Chem. 262:17703-11 (1987), and Vitaxin, described in International Patent Application WO 9833919 and in Wu et al., Proc. Natl. Acad. Sci. USA 95(11):6037-42 (1998); and antibodies directed against P- and E-selectins, pleiotropin and endosialin, endoglin, VEGF receptors, PDGF receptors, EGF receptors, FGF receptors, MMPs, and prostate specific membrane antigen (PSMA). Additional targets are described by E. Ruoslahti in Nature Reviews: Cancer, 2, 83-90 (2002).

Detail Description Paragraph:
[0096] Preferred routes of administration of the cell-surface targeted therapeutic agents of the present invention are by intravenous, interperitoneal, or subcutaneous injection including administration to veins or the lymphatic system. While the primary focus of the invention is on vascular-targeted agents, in principle, a targeted agent can be designed to focus on markers present in other fluids, body tissues, and body cavities, e.g. synovial fluid, ocular fluid, or spinal fluid. Thus, for example, an agent can be administered to spinal fluid, where an antibody targets a site of pathology accessible from the spinal fluid. Intrathecal delivery, that is, administration into the cerebrospinal fluid bathing the spinal cord and brain, may be appropriate for example, in the case of a target residing in the choroid plexus endothelium of the cerebral spinal fluid (CSF)-blood barrier.

L24: Entry 66 of 113 File: USPT Feb 26, 2002

DOCUMENT-IDENTIFIER: US 6350431 B1
TITLE: Compounds

Brief Summary Text (80):
In particular, the present invention provides a method of imaging the sentinel lymph node using a light-imaging contrast agent as described herein. Imaging the sentinel lymph node is of particular importance since this lymph node is found closest to the tumor site.

Brief Summary Text (135):
The vector group, V, can be selected from a wide variety of naturally occurring or synthetically prepared materials, including, but not limited to enzymes, amino acids, peptides, polypeptides, proteins, lipoproteins, glycoproteins, lipids, phospholipids, hormones, growth factors, steroids, vitamins, polysaccharides, lectins, toxins, nucleic acids (including sense and antisense oligonucleotides, peptide nucleic acids), haptens, avidin and derivatives thereof, biotin and derivatives thereof, antibodies (monoclonal and polyclonal), anti-antibodies, antibody fragments and antigenic materials (including proteins and carbohydrates). The vector group, V, can be also be selected from, but not limited to, components or products of viruses, bacteria, protozoa, fungi, parasites, rickettsia, molds, as well as animal and human blood, tissue and organ components. Furthermore, the vector group, V, can be a pharmaceutical drug or synthetic analog of any of the materials mentioned above as well as others known to one skilled in the art. Additional specific vector groups are described in WO 96/40285 which patent is incorporated herein in its entirety.

Brief Summary Text (182):
"Endothelial cells" or "endothelium" refers to an aggregate of cells and/or tissue which may be normal and/or diseased and which may comprise a single layer of flattened transparent endothelial cells that may be joined edge to edge or in an overlapping fashion to form a membrane. Endothelial cells are found on the free surfaces of the serous membranes, as part of the lining membrane of the heart, blood vessels, and lymphatics, on the surface of the brain and spinal cord, and in the anterior chamber of the eye.

Brief Summary Text (193):
Examples of monoclonal antibodies which may be employed as targeting vectors in the present compositions include CALAM 27, which is formed by immunizing BALB/c mice with whole human squamous cell carcinoma of the tongue and forming hybridomas by crossing extracted spleen cells with those of an NS1 syngeneic myeloma cell line. Gloanni, J. et al., Cancer Research, Vol. 47, pp. 4417-4424 (1987). CALAM is directed to surface epitopes of both normal and malignant epithelial cells. Normal lymph nodes generally do not contain cells expressing these epitopes. See Cancer Research, Vol. 47, pp. 4417-4424 (1987). Accordingly, chromophore polymers comprising this antibody can be used to target metastases in the lymph nodes. The monoclonal antibody 3C2 may be employed as a targeting vector for targeting malignant epithelial cells of serious ovarian carcinoma and endometrioid carcinoma. Another exemplary targeting vector is Mab 4C7 (se, Cancer Research, Vol. 45, 2358-2362, 1985) which may be used to target mucinous carcinoma, endometriod carcinoma and mesonephroid carcinoma. For targeting squamous cell carcinoma in head and neck

cancer, Mab E48 (Biological Abstract, Vol. 099 Issue. 066 Ref 082748) may be used as a targeting vector. For targeting malignant melanoma, the monoclonal antibody 225.28s (Pathol. Biol., Vol. 38 (8), pp. 866-869,1990) may be employed.

Brief Summary Text (291):
Administration of drugs and other agents by this route is often preferred due to enhanced patient compliance (for repeated dosing) and ease of administration. It is well known in the art that not every agent is bioavailable via this route; that is to say, that not all molecules are 1) chemically stable in the environs of the gut, 2) transportable across alimentary membranes for absorption into the blood/lymphatics, and 3) active even if accessible due to metabolic processes within the gut or possible solubility issues, etc. However, it is also known in the art, that alteration of the molecular structure to control the relative hydrophobicity of the molecule (i.e., partition coefficient between octanol and water; log(P)) within a preferred range can increase the oral availability of the agent.

Brief Summary Text (293):
The contrast agent can be injected into the vasculature prior to or during surgery. For detection of lymph nodes it can be injected into a lymph duct draining into the surgical area. Alternatively it may be applied during surgery as a topical ointment, a liquid, or a spray.

Brief Summary Text (301):
While the contrast agent compounds of the invention are particularly suited to intraoperative and post-surgical PDT and SDT use to facilitate visualization of tumor margins and optimize the surgical removal and PDT and SDT destruction of tumor tissues and cells, they can also be used as contrast agents in light imaging of tumor tissue, tumor cells and diseased lymph nodes. The light imaging technique may involve recording a photographic image of a tissue or organ surface illuminated with a light source that causes the contrast agent to exert a contrast enhancing effect and make the unhealthy tissue stand out more clearly from the surrounding healthy tissue, eg due to characteristic light absorption or fluorescence by the contrast agent. Such a photographic image may be recorded of an exposed surface (eg exposed during surgery) or may be recorded by insertion of an endoscope into a body cavity through a body orifice or through a surgical incision.

Brief Summary Text (316):
A preferred contrast agent for intraoperative CSLM, OCT, photoacoustic, acousto-optical, diffusive wave, time-resolved imaging, endoscopic, multiphoton excitation microscopy or visual observation techniques will have the following properties: it will consist of stabilized particles in aqueous or buffered solution. The particle size may be around 300 to 1300 nm (i.e., roughly equal to the wavelength of the light source). The refractive index of the particles will differ from that of body fluids such as blood and lymph by at least 0.01. The particles may be made of a chromophore polymer compound or may contain or be coated with a chromophore polymer compound, e.g., the particles may comprise a matrix material (e.g. a physiologically tolerable synthetic or non-synthetic polymer, such as an acrylate or polysaccharide) incorporating a chromophore polymer compound, a core of a chromophore polymer compound coated with a coating agent or encapsulated by a membrane forming material, or a core of a matrix material with a chromophore polymer compound coated on or attached to the particle surface. The particles may be solid, semi-solid or liquid and may be layered structures such as vesicles (e.g., micelles, liposomes and microballoons). The chromophore polymer compound used will preferably be a fluorescent material, particularly a material having an emission maximum in the near infrared range, especially in the range 650 to 900 nm. Optionally the particles may have suitable surface modifying agents, such as poly (ethylene glycol) to slow their uptake by macrophages in the body. Examples of suitable particulate agents are described in WO 96/23524. Optionally, the particles can be cells coated with the polymers of this invention. These coated cells can be

formed in the body with injected agents or externally from cells extracted from the body and then injected into the body.

Brief Summary Text (321):
When laser light with a wavelength between 600 and 1200 nm is reflected from the skin, the necessary changing pattern of light reflecting back to a light detector results largely from movement of blood cells within the dermis. However, speckle interferometry is best suited for determination of blood flow in vessels with diameters between 0.08 and 1 mm. Laser Doppler measurement is best used for blood vessels 0.08 mm and possibly smaller in size (Ul'Yanov, S. S.; Tuchin; Bednow; Brill, G. E.; Zakharova, E. I., "The Application of Speckle Interferometry for the Monitoring of Blood and Lymph Flow in Microvessels", Lasers in Medical Science, 1996, 11, 97-107). Light reflected from larger vessels, which lie deep within the dermis and in the underlying tissue, only serves to complicate the analysis of the light from the smaller vessels lying about 0.5 mm beneath the surface of the skin (Abbot, N. C.; Ferrell, W. R.; Lockhart, J. C.; Lowe, J. G., "Laser Doppler Perfusion Imaging of Skin Blood Flow Using Red and Near-Infrared Sources", J. Invest. Dermatol., 1996, 107, 882-886).

Brief Summary Text (325):
Therapeutic application using these compounds can be achieved in the form of cytotoxic application of light in the form of photodynamic therapy wherein the tissues to be treated or destroyed are treated first with contrast agents which are allowed to intimately associate with the tissue and then by irradiation with light which is absorbed by the contrast agents in vivo, optionally in the presence of oxygen in the blood or in oxygenated saline solution, or in oxygenated plasma, or oxygenated lymph fluid and the like.

Brief Summary Text (326):
Therapeutic application using these compounds can sometimes be achieved with sonodynamic therapy wherein the tissues to be treated or destroyed are treated first with contrast agents which are allowed to intimately associate with the tissue and then by sonication with high frequency sound such as ultrasound optionally in the presence of oxygen in the blood or in oxygenated saline solution, or in oxygenated plasma, or oxygenated lymph fluid and the like.

Detailed Description Text (81):
This emulsion (Sudan III) may be injected peri-tumorally to migrate to the regional draining lymph nodes for ease of resection. (This is currently done in melanoma and breast cancer. These nodes are important for staging the progress of the disease and planning patient management). This emulsion may also make the histopathology easier and more accurate by staining the healthy tissue thereby making the disease tissue more obvious as a filling defect to the emulsion. Further, the emulsion may be administered iv to effect a marking of the healthy tissue of the liver and spleen and other organs which are MPS rich. This will provide visible contrast between the healthy tissue and diseased tissue, lesions, malformations, etc., for ease in surgical resection. Even areas with low or blocked blood flow would be contrasted with normal vascular beds via the content of the blood of the Sudan III emulsion (P79 has been shown to afford prolonged circulation to liposomes and emulsions in corresponding X-ray contrast formulations).

Detailed Description Text (85):
A sterile filtered suspension of fluorescein prepared in this manner was administered subcutaneously to an anesthetized dog with a cannulated thoracic duct to monitor lymph flow and contents. The fluorescein may be detected in the lymph fluid indicating that the dye nanoparticles are passing through the lymphatics thereby marking the lymph nodes as required to aid in the visual identification of lymph nodes for resection and use in cancer staging.

CLAIMS:

28. A method as claimed in claim 27 wherein said part of said body is the sentinel lymph node.

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DOCUMENT-IDENTIFIER: US 6077499 A
TITLE: Targeted combination immunotherapy of cancer

Detailed Description Text (22):
The targeting moiety may be, for example, an antibody or an antigen binding antibody fragment. Monoclonal antibodies are preferred because of their high specificities. They are readily prepared by what are now considered conventional procedures of immunization of mammals with immunogenic antigen preparation, fusion of immune lymph or spleen cells with an immortal myeloma cell line, and isolation of specific hybridoma clones. More unconventional methods of preparing monoclonal antibodies also are contemplated, such as interspecies fusions and genetic engineering manipulations of hypervariable regions, since it is primarily the antigen specificity of the antibodies that affects their utility in the present invention. It will be appreciated that newer techniques for production of monoclonals can also be used, e.g., human monoclonals, interspecies monoclonals, chimeric (e.g., human/mouse) monoclonals, genetically engineered antibodies and the like.

Detailed Description Text (28):
contents of all of which are incorporated herein by reference in their entirety. In particular, antibodies against an antigen, e.g., a gastrointestinal, lung, breast, prostate, ovarian, testicular, brain or lymphatic tumor, a sarcoma or a melanoma, are advantageously used.

Detailed Description Text (65):
From the above description, it will be evident that the invention can be used advantageously with the pre-targeting and amplification methods described in the above-cited U.S. patents and patent applications. For example, the first antibody conjugate may comprise a polymer to which are attached a plurality of streptavidin moieties, providing an increased number of binding sites for the subsequently administered biotin to bind, as described in U.S. Pat. No. 5,482,698.